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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/765,644	01/22/2001	Michael Eisenbach-schwartz	EIS-SCHWARTZ=13B	6853

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EXAMINER
BUNNER, BRIDGET E

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/765,644	EISENBACH-SCHWARTZ ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *2-5,8,14-18,21,23-26,29 and 35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,7,9-13,19,20,22,27,28,30-34 and 40-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-42* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 21 January 2003 (Paper No. 13) and 02 January 2003 (Paper No. 12) have been entered in full. Claims 40-42 are added and claims 1-3, 6-19, 23-24, 27-40, and 42 are amended.

Election/Restrictions

Applicant's election with traverse of Group II, claims 1, 6-22, 27-30, and 31-39, drawn to a method of preventing or inhibiting neuronal degeneration which comprises administering Copl or Copl related protein in Paper No. 12 (02 January 2003) is acknowledged. The traversal, especially between Groups I and II, is on the ground(s) that the dichotomy between *in vivo* and *in vitro* activation of the T cells is not a true dichotomy between patentably distinct inventions. Applicant argues that to better emphasize this point, new claim 40 has been added which is a true generic claim. Applicant asserts that it does not matter whether T cell accumulation is caused by active administration of Copl or by passive administration of activated T cell directly. This is not found persuasive because Group I requires search and consideration of efficacy of T cell administration to reduce neuronal degeneration. Group II requires search and consideration of Cop 1 protein administration to reduce neuronal degeneration. Groups I and II are different methods that require different ingredients (T cells vs. Cop 1 protein) and may be classified separately, for example in class 424, subclass 93.7 and class 514, subclass 2, respectively (see MPEP § 803.02 and § 806.04). The search and examination of both groups together represents a burden to the examiner, regardless of any similarity in reagents or steps. Also, although claim 40 may be a generic claim, it will be searched to the extent that it reads upon the elected invention

(administration of Cop 1) for the reasons set forth above. Furthermore, Applicant contends that the restriction between Groups I and II (prevention or inhibition of neuronal degeneration) and Groups III and IV (promotion of nerve regeneration) should be withdrawn. Applicant submits that the only difference lies in the preamble of claim 1 and that the ingredients, process steps, and endpoints are substantially the same. Applicant states that usually, if nerve regeneration is promoted, then neuronal degeneration will simultaneously be prevent or inhibited and vice versa. This is not found persuasive. The methods are separable as evidenced by the following literature references which establish a separate status in the art of axonal regeneration and axonal degeneration which are diametrically opposed processes and are patentably distinct as evidenced by Plata-Salaman et al. (Peptides 12(3): 653-663, 1991), George et al. (J Neurosci 15(10) : 6445-6452, 1995), Petrovich et al. (Neurol Res19(5) : 551-554, 1997), Bradbury et al. (Eur J Neurosci 10(10) :3058-3068, 1998), Pan et al. (Neurosci Biobehav Rev 21(5) : 603-613, 1997), and Wang et al. (J Neuropath Exp Neurol 59(7): 599-606, 2000.

The requirement is still deemed proper and is therefore made FINAL.

Claims 2-5, 8, 14-18, 21, 23-26, 29, and 35-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 12 (02 January 2003).

Claims 1, 6-7, 9-13, 19-20, 22, 27-28, 30-34, and 40-42 are under consideration in the instant application and read upon the elected group of administration of COP 1 and the species CNS, Cop 1, injury, spinal cord injury, and ala glu lys tyr.

Specification

1. The disclosure is objected to because of the following informalities:

1a. An updated status of the parent nonprovisional application should be included in the first sentence of the specification. A statement reading "This is a continuation-in-part of co-pending U.S. application no. 09/620,216, filed July 20, 2000, abandoned, which is a continuation-in-part of U.S. application no. 09/487,793, filed January 20, 2000, abandoned..." should be entered.

1b. Patent applications are referenced in the disclosure (pg 55, line 12). The status of the applications must be updated.

1c. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "A METHOD FOR REDUCING SECONDARY NEURONAL DEGENERATION BY ADMINISTERING COPOLYMER 1".

Appropriate correction is required.

Claim Objections

2. Claims 1, 6-7, 9-12, 19-20, 22, 27-28, 30-33, and 40-42 are objected to because of the following informalities:

Claims 1, 6-7, 9-12, 19-20, 22, 27-28, 30-33, and 40-42 recite a non-elected groups and species.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims, 1, 6-7, 9-13, 19-20, 22, 27-28, 30-34, and 40-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing secondary neuronal degeneration in the central nervous system (CNS) to ameliorate the degenerative effects of crush-injured CNS nerve comprising administering to an individual in need thereof a composition consisting of Copolymer 1 wherein the Copolymer 1 reduces secondary neuronal degeneration, does not reasonably provide enablement for a method for reducing neuronal degeneration in the central nervous system or a method for reducing neuronal degeneration caused by all possible injuries which comprises administering to an individual in need thereof an effective amount of at least Copolymer 1, wherein the individual in need is other than one with multiple sclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are also recite that Copolymer 1 is a random copolymer that cross-reacts functionally with myelin basic protein (MBP) and is capable of competing with MBP ion the MHC class II molecule in antigen presentation. The claims recite that Copolymer 1 (Cop 1) is administered in a manner which promotes active immunization of the individual so as to build up a critical T cell response. The claims recite that the random copolymer consists of four different amino acids: alanine, glutamic acid, lysine, and tyrosine. The claims also recite that the injury is spinal cord injury and that the injury is other than autoimmune disease.

The specification teaches that anesthetized rats are subjected to mild crush injury of the optic nerve and immediately vaccinated with Cop 1 in IFA, with a booster give two days later (pg 67,

lines 27-28 through pg 68, lines 1-2). The specification also discloses that after two weeks, the retinal ganglion cells (RGCs) are retrogradely labeled and five days later, the rats are killed and their retinas excised. The specification indicates that rats vaccinated with Cop 1 in IFA show evidence of protection of optic nerve fibers from secondary degeneration compared to that in control rats injected with PBS in IFA (pg 68, lines 2-6; Figure 3).

However, the specification does not teach any methods or working examples that indicate a reduction of "primary" neuronal degeneration in CNS by administration of Cop 1 to an individual. The specification teaches that "a catastrophic consequence of central nervous system injury is that the primary damage is often compounded by the gradual secondary loss of adjacent neurons that apparently were undamaged, or only marginally damaged by the initial injury"(pg 3, last ¶). The specification also discloses that "neurons in the central nervous system do not undergo spontaneous regeneration following an injury" (pg 5, ¶ 2). As echoed by Jackowski, it is well known in this unpredictable art that regeneration does not occur in the CNS either because processes fail to grow the necessary distance, they are in competition with other nearby neuronal processes not derived from the affected nerve, astrocytic scarring blocks axonal elongation, or because of misdirected axonal growth (e.g., see Jackowski, Brit J Neurosurgery 9: 303-317, 1995; specifically pgs. 309-310 and pg. 305, last ¶). Accordingly, because of the lack of guidance provided by the specification as to how one can rescue dead or dying cells instantaneously affected, for example, by a head injury, there is no nexus that merely administering Cop 1 to an individual in need thereof can reasonably be extrapolated to successfully treat any human subject experiencing *"primary"* neuronal degeneration, as claimed, without undue experimentation to determine such. The examples in the specification of the

instant application only indicate that administration of Cop 1 reduces *secondary* neuronal degeneration caused by crush-injured CNS nerve (see pg 67-68 and 84-85).

Additionally, the specification teaches that Cop 1 may be used to inhibit secondary degeneration which may otherwise follow primary nervous system injury, e.g., closed head injuries and blunt trauma (pg 44, ¶ 2). However, this is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. As discussed above, the specification only teaches that rats vaccinated with Cop 1 in IFA show evidence of protection of optic nerve fibers from secondary degeneration compared to that in control rats injected with PBS in IFA (pg 68, lines 2-6; Figure 3). Therefore, undue experimentation would be required of the skilled artisan to determine the optimal dosage, duration, and route of administration of Cop 1 to reduce the neuronal degeneration caused by all possible injuries. The scope of the claims (see claims 19 and 22) also encompass a reduction of neuronal degeneration caused by injury other than multiple sclerosis and other than an autoimmune disease. The scope encompasses injuries not expected to be commensurate with crush injury, such as gunshot wounds, damages caused by surgery, blunt trauma, spinal cord injury, and closed head injuries (pg 44, ¶ 2). The effects encompassed by these injuries are broad and may include for example, paralysis, blurred vision, blindness, pain, sensory deficits, memory loss, cognitive deficits, and behavioral changes, which effects are not commensurate with crush injury. The etiology and pathology of crush injury is largely dissimilar from other injuries (particularly of the CNS) and the skilled artisan would not be able to predict that administration of Cop 1 would be beneficial for all possible injuries.

Furthermore, the specification does not teach any methods or working examples that indicate T cells activated by Cop 1 accumulate at the site of neuronal degeneration in an individual after administration of the Cop 1 protein. Undue experimentation would be required of the skilled artisan to determine if T cells accumulate at the site of neuronal degeneration after administration of Cop 1 and to test the T cells *in vivo* or *ex vivo* to determine if they are specific for Cop 1. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed".

It is also noted that a broad, reasonable interpretation of the claims encompasses such diseases as Alzheimer's disease, Parkinson's disease, and Huntington's disease, among others, which have proven to be recalcitrant to treatment in the art (see for example, Halliday et al., Clin Exp Pharmacol Physiol 27: 1-8, 2000; Steece-Collier et al., Proc Natl Acad Sci USA 99(22): 13972-13974, 2002; Feigin et al. Curr Opin Neurol 15: 483-489, 2002). Therefore, undue experimentation would be required of the skilled artisan to reduce neuronal degeneration in patients with a neurodegenerative disorder by administration of Cop 1.

Due to the large quantity of experimentation necessary to reduce primary neuronal degeneration in CNS, to reduce neuronal degeneration caused by all possible injuries, to determine whether or not T cells activated against Cop 1 accumulate at the site of neuronal degeneration and to treat neurodegenerative diseases, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of Cop 1 administration

on all possible injuries and on T cell accumulation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1, 6-7, 9-13, 19-20, 22, 27-28, 30-34, and 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1, 6-7, 9-13, 19-20, 22, 27-28, and 30-34 are indefinite because the claim does not have a step that clearly relates back to the preamble. For example, there is no step indicating that administration of Cop-1 reduces neuronal degeneration.

8. Claims 40-42 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: The administration of Copolymer 1 to an individual to cause activated T cells to accumulate at the site of neuronal degeneration.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Methods of using Cop 1:

Teitelbaum et al. Proc Natl Acad Sci USA 96: 3842-3847, 1999.
Konfino et al. U.S. Patent 6,342,476
Arnon et al. U.S. Patent 6,214,791
Schori et al. Proc Natl Acad Sci USA 98: 3398-3403, 2001.
Kipnis et al. Proc Natl Acad Sci USA 97 : 7446-7451, 2000.
Schwartz, M. Drug Develop Res 50(3-4): 223-225, 2000.
Arnon et al. J Neurol. 243(4 Suppl 1):S8-13, 1996.
Teitelbaum D et al. Cell Mol Life Sci. 53(1):24-28, 1997.
Kipnis et al. Trends Molec Med 8(7): 319-323, 2002.
Miller, A et al. J Neuroimmunol. 92(1-2):113-121, 1998.

Copolymer :

Teitelbaum et al. U.S. Patent 3,849,550

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 872-9305.

BEB BEB
Art Unit 1647
April 9, 2003

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER